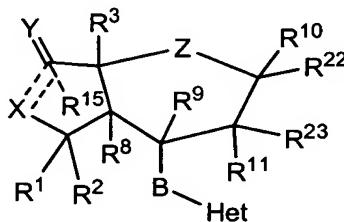


5 We claim:

1. A method of treating a therapeutic condition comprising administering to a mammal in need of such treatment an effective amount of at least one compound of the formula:

10



or a pharmaceutically acceptable isomer, salt, solvate or co-crystal form thereof, wherein:

15 Z is $-(CH_2)_n-$, when R^{10} is absent, or

when R^3 is absent;

the single dotted line adjacent to R^{34} ----- represents an optional double bond;

the double dotted lines adjacent to X ===== together represent an optional single bond;

20

n is 0-2;

R¹ and R² are independently selected from the group consisting of H, C₁-C₆ alkyl, fluoro(C₁-C₆)alkyl, difluoro(C₁-C₆)alkyl, trifluoro-(C₁-C₆)alkyl, C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, aryl(C₁-C₆)alkyl, aryl(C₂-C₆)alkenyl, heteroaryl(C₁-C₆)alkyl, heteroaryl(C₂-C₆)alkenyl, hydroxy-(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, amino-(C₁-C₆)alkyl, aryl and thio(C₁-C₆)alkyl; or R¹ and R² together

25

form a =O group;

R³ is H, hydroxy, C₁-C₆ alkoxy, -NR¹⁸R¹⁹, -SOR¹⁶, -SO₂R¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁸R¹⁹, C₁-C₆ alkyl, halogen, fluoro(C₁-C₆)alkyl, difluoro(C₁-C₆)alkyl, trifluoro(C₁-C₆)alkyl, C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, aryl(C₁-C₆)alkyl, aryl(C₂-C₆)alkenyl,

- 5 C₆)alkenyl, heteroaryl(C₁-C₆)alkyl, heteroaryl(C₂-C₆)alkenyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, aryl, thio(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl or (C₁-C₆)alkylamino(C₁-C₆)alkyl;
R³⁴ is (H, R³), (H, R⁴³), =O or =NOR¹⁷ when the optional double bond adjacent to R³⁴ is absent; R³⁴ is R⁴⁴ when the double bond is present;
- 10 Het is a mono-, bi- or tricyclic heteroaromatic group of 5 to 14 atoms comprised of 1 to 13 carbon atoms and 1 to 4 heteroatoms independently selected from the group consisting of N, O and S, wherein a ring nitrogen can form an N-oxide or a quaternary group with a C₁-C₄ alkyl group, wherein Het is attached to B by a carbon atom ring member of Het, and wherein the Het group is substituted by
- 15 1 to 4 moieties, W, independently selected from the group consisting of H; C₁-C₆ alkyl; fluoro(C₁-C₆)alkyl; difluoro(C₁-C₆)alkyl; trifluoro-(C₁-C₆)-alkyl; C₃-C₇ cycloalkyl; heterocycloalkyl; heterocycloalkyl substituted by C₁-C₆ alkyl, C₂-C₆ alkenyl, OH-(C₁-C₆)alkyl, or =O; C₂-C₆ alkenyl; R²¹-aryl(C₁-C₆)alkyl; R²¹-aryl-(C₂-C₆)-alkenyl; R²¹-aryloxy; R²¹-aryl-NH-; heteroaryl(C₁-C₆)alkyl; heteroaryl(C₂-
- 20 C₆)-alkenyl; heteroaryloxy; heteroaryl-NH-; hydroxy(C₁-C₆)alkyl; dihydroxy(C₁-C₆)alkyl; amino(C₁-C₆)alkyl; (C₁-C₆)alkylamino-(C₁-C₆)alkyl; di-((C₁-C₆)alkyl)-amino(C₁-C₆)alkyl; thio(C₁-C₆)alkyl; C₁-C₆ alkoxy; C₂-C₆ alkenyloxy; halogen; -NR⁴R⁵; -CN; -OH; -COOR¹⁷; -COR¹⁶; -OSO₂CF₃; -CH₂OCH₂CF₃; (C₁-C₆)alkylthio; -C(O)NR⁴R⁵; -OCHR⁶-phenyl; phenoxy-(C₁-C₆)alkyl; -NHCOR¹⁶; -
- 25 NHSO₂R¹⁶; biphenyl; -OC(R⁶)₂COOR⁷; -OC(R⁶)₂C(O)NR⁴R⁵; (C₁-C₆)alkoxy; -C(=NOR¹⁷)R¹⁸; C₁-C₆ alkoxy substituted by (C₁-C₆)alkyl, amino, -OH, COOR¹⁷, -NHCOOR¹⁷, -CONR⁴R⁵, aryl, aryl substituted by 1 to 3 moieties independently selected from the group consisting of halogen, -CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy and -COOR¹⁷, aryl wherein adjacent carbons form a ring with a methylenedioxy group, -C(O)NR⁴R⁵ or heteroaryl; R²¹-aryl; aryl wherein adjacent carbons form a ring with a methylenedioxy group; R⁴¹-heteroaryl; and heteroaryl wherein adjacent carbon atoms form a ring with a C₃-C₅ alkylene group or a methylenedioxy group;

5 R⁴ and R⁵ are independently selected from the group consisting of H, C1-C6 alkyl, phenyl, benzyl and C3-C7 cycloalkyl, or R⁴ and R⁵ together are -(CH₂)₄-, -(CH₂)₅- or -(CH₂)₂NR⁷-(CH₂)₂- and form a ring with the nitrogen to which they are attached;

10 R⁶ is independently selected from the group consisting of H, C1-C6 alkyl, phenyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl and amino(C₁-C₆)alkyl;

R⁷ is H or (C₁-C₆)alkyl;

15 R⁸, R¹⁰ and R¹¹ are independently selected from the group consisting of R¹ and -OR¹, provided that when the optional double bond is present, R¹⁰ is absent;

R⁹ is H, OH, C₁-C₆ alkoxy, halogen or halo(C₁-C₆)alkyl;

B is -(CH₂)_n3-, -CH₂-O-, -CH₂S-, -CH₂-NR⁶-, -C(O)NR⁶-, -NR⁶C(O)-,



, cis or trans -(CH₂)_nCR¹²=CR^{12a}(CH₂)_n5- or -(CH₂)_nC≡C(CH₂)_n5-,

wherein n₃ is 0-5, n₄ and n₅ are independently 0-2, and R¹² and R^{12a} are

20 independently selected from the group consisting of H, C₁-C₆ alkyl and halogen;

X is -O- or -NR⁶- when the double dotted lines adjacent to X represent a single bond, or X is H, -OH or -NHR²⁰ when the bond is absent;

25 Y is =O, =S, (H, H), (H, OH) or (H, C₁-C₆ alkoxy) when the double dotted lines adjacent to X represent a single bond, or when the bond is absent, Y is =O, =NOR¹⁷, (H, H), (H, OH), (H, SH), (H, C₁-C₆ alkoxy) or (H, -NHR⁴⁵);

R¹⁵ is absent when the double dotted lines adjacent to X represent a single bond; R¹⁵ is H, C₁-C₆ alkyl, -NR¹⁸R¹⁹ or -OR¹⁷ when said single bond is absent;

or Y is or and R¹⁵ is H or C₁-C₆ alkyl;

R¹⁶ is C₁-C₆ lower alkyl, phenyl or benzyl;

5 R¹⁷, R¹⁸ and R¹⁹ are independently selected from the group consisting of H, C₁-C₆ alkyl, phenyl, benzyl;

R²⁰ is H, C₁-C₆ alkyl, phenyl, benzyl, -C(O)R⁶ or -SO₂R⁶;

R²¹ is 1 to 3 moieties independently selected from the group consisting of hydrogen, -CN, -CF₃, -OCF₃, halogen, -NO₂, C₁-C₆ alkyl, C₁-C₆alkoxy,

10 (C₁-C₆)alkylamino, di-((C₁-C₆)alkyl)amino, amino(C₁-C₆)alkyl, (C₁-C₆)-alkylamino(C₁-C₆)alkyl, di-((C₁-C₆)alkyl)-amino(C₁-C₆)alkyl, hydroxy-(C₁-C₆)alkyl, -COOR¹⁷, -COR¹⁷, -NHCOR¹⁶, -NHSO₂R¹⁶, -NHSO₂CH₂CF₃, heteroaryl or -C(=NOR¹⁷)R¹⁸;

15 R²² and R²³ are independently selected from the group consisting of hydrogen, R²⁴-(C₁-C₁₀)alkyl, R²⁴-(C₂-C₁₀)alkenyl, R²⁴-(C₂-C₁₀)alkynyl, R²⁷-hetero-cycloalkyl, R²⁵-aryl, R²⁵-aryl(C₁-C₆)alkyl, R²⁹-(C₃-C₇)cycloalkyl, R²⁹-(C₃-C₇)cycloalkenyl, -OH, -OC(O)R³⁰, -C(O)OR³⁰, -C(O)R³⁰, -C(O)NR³⁰R³¹, -NR³⁰R³¹, -NR³⁰C(O)R³¹, -NR³⁰C(O)NR³¹R³², -NHSO₂R³⁰, -OC(O)NR³⁰R³¹, R²⁴-(C₁-C₁₀)alkoxy, R²⁴-(C₂-C₁₀)-alkenyloxy, R²⁴-(C₂-C₁₀)alkynyloxy,

20 R²⁷-heterocycloalkyloxy, R²⁹-(C₃-C₇)cycloalkyloxy, R²⁹-(C₃-C₇)cyclo-alkenyloxy, R²⁹-(C₃-C₇)cycloalkyl-NH-, -CH₂-O-CH₂-phenyl, -NHSO₂NHR¹⁶ and -CH(=NOR¹⁷);

or R²² and R¹⁰ together with the carbon to which they are attached, or R²³ and R¹¹ together with the carbon to which they are attached, independently form a R⁴²-substituted carbocyclic ring of 3-10 atoms, or a R⁴²-substituted heterocyclic ring of 4-10 atoms wherein 1-3 ring members are independently selected from the group consisting of -O-, -NH- and -SO₂-₂, provided that when R²² and R¹⁰ form a ring, the optional double bond is absent;

25 R²⁴ is 1, 2 or 3 moieties independently selected from the group consisting of hydrogen, halogen, -OH, (C₁-C₆)alkoxy, R³⁵-aryl, (C₁-C₁₀)-alkyl-C(O)-, (C₂-C₁₀)-alkenyl-C(O)-, (C₂-C₁₀)alkynyl-C(O)-, heterocycloalkyl, R²⁶-(C₃-C₇)cycloalkyl, R²⁶-(C₃-C₇)cycloalkenyl, -OC(O)R³⁰, -C(O)OR³⁰, -C(O)R³⁰, -C(O)NR³⁰R³¹, -NR³⁰R³¹, -NR³⁰C(O)R³¹, -NR³⁰C(O)NR³¹R³², -NHSO₂R³⁰, -OC(O)NR³⁰R³¹, R²⁴-(C₂-C₁₀)-alkenyloxy, R²⁴-(C₂-C₁₀)alkynyloxy, R²⁷-heterocycloalkyloxy, R²⁹-(C₃-C₇)-cycloalkyloxy, R²⁹-(C₃-C₇)cyclo-alkenyloxy, R²⁹-(C₃-C₇)cycloalkyl-NH-, 35 -NHSO₂NHR¹⁶ and -CH(=NOR¹⁷);

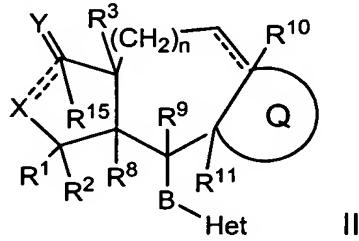
- 5 R^{25} is 1, 2 or 3 moieties independently selected from the group consisting of hydrogen, heterocycloalkyl, halogen, -COOR³⁶, -CN, -C(O)NR³⁷R³⁸, -NR³⁹C(O)R⁴⁰, -OR³⁶, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-C₁-C₆)alkyl, (C₁-C₆)alkyl(C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl(C₃-C₇)cycloalkyl(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl,
- 10 (C₁-C₆)alkoxy(C₁-C₆)alkyl, and R⁴¹-heteroaryl; or two R²⁵ groups on adjacent ring carbons form a fused methylenedioxy group;
- R²⁶ is 1, 2, or 3 moieties independently selected from the group consisting of hydrogen, halogen and (C₁-C₆)alkoxy;
- R²⁷ is 1, 2 or 3 moieties independently selected from the group consisting of hydrogen, R²⁸-(C₁-C₁₀)alkyl, R²⁸-(C₂-C₁₀)alkenyl, R²⁸-(C₂-C₁₀)alkynyl;
- 15 R²⁸ is hydrogen, -OH or (C₁-C₆)alkoxy;
- R²⁹ is 1, 2 or 3 moieties independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, -OH, (C₁-C₆)alkoxy and halogen;
- R³⁰, R³¹ and R³² are independently selected from the group consisting of hydrogen, (C₁-C₁₀)-alkyl, (C₁-C₆)alkoxy(C₁-C₁₀)-alkyl, R²⁵-aryl(C₁-C₆)-alkyl, R³³-(C₃-C₇)cycloalkyl, R³⁴-(C₃-C₇)cycloalkyl(C₁-C₆)alkyl, R²⁵-aryl, heterocycloalkyl, heteroaryl, heterocycloalkyl(C₁-C₆)alkyl and heteroaryl(C₁-C₆)alkyl;
- R³³ is hydrogen, (C₁-C₆)alkyl, OH-(C₁-C₆)alkyl or (C₁-C₆)alkoxy;
- R³⁵ is 1 to 4 moieties independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, -OH, halogen, -CN, (C₁-C₆)alkoxy, trihalo(C₁-C₆)alkoxy, (C₁-C₆)alkylamino, di((C₁-C₆)alkyl)amino, -OCF₃, OH-(C₁-C₆)alkyl, -CHO, -C(O)(C₁-C₆)-alkylamino, -C(O)di((C₁-C₆)alkyl)amino, -NH₂, -NHC(O)(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)C(O)(C₁-C₆)alkyl;
- R³⁶ is hydrogen, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, dihalo(C₁-C₆)alkyl or trifluoro(C₁-C₆)alkyl;
- R³⁷ and R³⁸ are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, aryl(C₁-C₆)alkyl, phenyl and (C₃-C₁₅)cycloalkyl, or R³⁷ and R³⁸ together are -(CH₂)₄-, -(CH₂)₅- or -(CH₂)₂-NR³⁹-(CH₂)₂- and form a ring with the nitrogen to which they are attached;
- 35 R³⁹ and R⁴⁰ are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, aryl(C₁-C₆)alkyl, phenyl and (C₃-C₁₅)-cycloalkyl, or R³⁹ and

- 5 R⁴⁰ in the group -NR³⁹C(O)R⁴⁰, together with the carbon and nitrogen atoms to which they are attached, form a cyclic lactam having 5-8 ring members;
- R⁴¹ is 1 to 4 moieties independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylamino, di((C₁-C₆)alkyl)amino, -OCF₃, OH-(C₁-C₆)alkyl, -CHO and phenyl;
- 10 R⁴² is 1 to 3 moieties independently selected from the group consisting of hydrogen, -OH, (C₁-C₆)alkyl and (C₁-C₆)alkoxy;
- R⁴³ is -NR³⁰R³¹, -NR³⁰C(O)R³¹, -NR³⁰C(O)NR³¹R³², -NHSO₂R³⁰ or -NHCOOR¹⁷;
- R⁴⁴ is H, C₁-C₆ alkoxy, -SOR¹⁶, -SO₂R¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁸R¹⁹,
- 15 C₁-C₆ alkyl, halogen, fluoro(C₁-C₆)alkyl, difluoro(C₁-C₆)alkyl, trifluoro(C₁-C₆)alkyl, C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, aryl(C₁-C₆)alkyl, aryl(C₂-C₆)alkenyl, heteroaryl(C₁-C₆)alkyl, heteroaryl(C₂-C₆)alkenyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, aryl, thio(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl or (C₁-C₆)alkylamino(C₁-C₆)alkyl; and
- 20 R⁴⁵ is H, C₁-C₆ alkyl, -COOR¹⁶ or -SO₂,
- wherein said therapeutic condition is a cardiovascular or circulatory disease or condition, an inflammatory disease or condition, a respiratory tract disease or condition, cancer, acute renal failure, glomerulonephritis, astrogliosis, a fibrotic disorder of the liver, kidney, lung or intestinal tract, Alzheimer's disease, diabetes, diabetic neuropathy, rheumatoid arthritis, neurodegenerative disease, neurotoxic disease, systemic lupus erythematosus, multiple sclerosis, osteoporosis, glaucoma, macular degeneration, psoriasis, radiation fibrosis, endothelial dysfunction, a wound or a spinal cord injury, or a symptom or result thereof.
- 30 2. The method of claim 1 wherein the cardiovascular or circulatory disease or condition is atherosclerosis, restenosis, hypertension, acute coronary syndrome, angina pectoris, arrhythmia, heart disease, heart failure, myocardial infarction, thrombotic or thromboembolic stroke, a peripheral vascular disease, deep vein thrombosis, venous thromboembolism, a cardiovascular disease associated with hormone replacement therapy, disseminated intravascular coagulation syndrome, renal ischemia, cerebral
- 35

- 5 stroke, cerebral ischemia, cerebral infarction, migraine, renal vascular homeostasis or erectile dysfunction.
- 10 3. The method of claim 1 wherein the inflammatory disease or condition is irritable bowel syndrome, Crohn's disease, nephritis or a radiation- or chemotherapy- induced proliferative or inflammatory disorder of the gastrointestinal tract, lung, urinary bladder, gastrointestinal tract or other organ.
- 15 4. The method of claim 1 wherein the respiratory tract disease or condition is reversible airway obstruction, asthma, chronic asthma, bronchitis or chronic airways disease.
- 20 5. The method of claim 1 wherein the cancer is renal cell carcinoma or an angiogenesis related disorder.
- 25 6. The method of claim 1 wherein the neurodegenerative disease is Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease or Wilson's disease.
- 30 7. The method of claim 1 further comprising administering at least one therapeutically effective agent useful in the treatment of inflammation, rheumatism, asthma, glomerulonephritis, osteoporosis, neuropathy and/or malignant tumors, angiogenesis related disorders, cancer, disorders of the liver, kidney or lung, melanoma, renal cell carcinoma, renal disease, acute renal failure, chronic renal failure, renal vascular homeostasis, glomerulonephritis, chronic airways disease, bladder inflammation, neurodegenerative and/or neurotoxic diseases, conditions, or injuries, radiation fibrosis, endothelial dysfunction, periodontal diseases or wounds.
- 35 8. The method of claim 7 further comprising administering at least two therapeutically effective agents.

5

9. A method of treating a therapeutic condition comprising administering to a mammal in need of such treatment an effective amount of at least one compound of the formula:



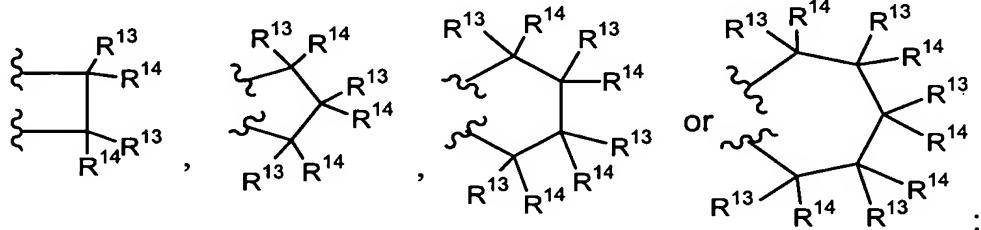
- 10 or a pharmaceutically acceptable isomer, salt, solvate or co-crystal form thereof, wherein:

the double dotted lines adjacent to X :::::: together represent an optional single bond;

- 15 the single dotted line adjacent to R¹⁰ ----- represents an optional double bond;

n is 0-2;

Q is



R¹ and R² are independently selected from the group consisting of H,

- 20 (C₁-C₆)alkyl, fluoro(C₁-C₆)alkyl-, difluoro(C₁-C₆)alkyl-, trifluoro-(C₁-C₆)alkyl-, (C₃-C₆)cycloalkyl, (C₂-C₆)alkenyl, hydroxy-(C₁-C₆)alkyl-, and amino(C₁-C₆)alkyl-;

R³ is H, hydroxy, (C₁-C₆)alkoxy, -SOR¹⁶, -SO₂R¹⁷, -C(O)OR¹⁷,

-C(O)NR¹⁸R¹⁹, -(C₁-C₆)alkyl-C(O)NR¹⁸R¹⁹, (C₁-C₆)alkyl, halogen,

fluoro(C₁-C₆)alkyl-, difluoro(C₁-C₆)alkyl-, trifluoro(C₁-C₆)alkyl-, (C₃-C₆)cycloalkyl,

- 25 (C₃-C₆)-cycloalkyl-(C₁-C₆)alkyl-, (C₂-C₆)alkenyl, aryl(C₁-C₆)alkyl-,

aryl(C₂-C₆)alkenyl-, heteroaryl(C₁-C₆)alkyl-, heteroaryl(C₂-C₆)alkenyl-,

hydroxy(C₁-C₆)-alkyl-, -NR²²R²³, NR²²R²³-(C₁-C₆)alkyl-, aryl, thio(C₁-C₆)alkyl-,

- 5 $(C_1-C_6)alkyl-thio(C_1-C_6)alkyl$ -, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$ -,
 $NR^{18}R^{19}-C(O)-(C_1-C_6)alkyl$ - or $(C_3-C_6)cycloalkyl-(C_1-C_6)alkyl$ -;
 Het is a mono- or bi-cyclic heteroaryl group of 5 to 10 atoms comprised of 1
 to 9 carbon atoms and 1 to 4 heteroatoms independently selected from the group
 consisting of N, O and S, wherein a ring nitrogen can form an N-oxide or a
10 quaternary group with a $(C_1-C_4)alkyl$ group, wherein Het is attached to B by a
 carbon atom ring member of said Het, and wherein the Het group is substituted by
 W;
 W is 1 to 4 moieties independently selected from the group consisting of H,
 $(C_1-C_6)alkyl$, fluoro $(C_1-C_6)alkyl$ -, difluoro $(C_1-C_6)alkyl$ -, trifluoro $(C_1-C_6)alkyl$ -,
15 $(C_3-C_6)cycloalkyl$, hydroxy $(C_1-C_6)alkyl$ -, dihydroxy $(C_1-C_6)alkyl$ -,
 $NR^{25}R^{26}(C_1-C_6)alkyl$ -, thio $(C_1-C_6)alkyl$ -, -OH, $(C_1-C_6)alkoxy$, halogen, $-NR^4R^5$,
 - $C(O)OR^{17}$, - COR^{16} , $(C_1-C_6)alkylthio$ -, $R^{21-}aryl$, $R^{21-}aryl(C_1-C_6)alkyl$ -, aryl wherein
 adjacent ring carbons in said aryl, along with two O atoms, form a methylenedioxy
 group, and $R^{21-}heteroaryl$;
20 R^4 and R^5 are independently selected from the group consisting of H,
 $(C_1-C_6)alkyl$, phenyl, benzyl and $(C_3-C_6)cycloalkyl$, or R^4 and R^5 taken together are
 $-(CH_2)_4$ -, $-(CH_2)_5$ - or $-(CH_2)_2NR^7-(CH_2)_2$ - and form a ring with the nitrogen to
 which they are attached;
 R^6 is H, $(C_1-C_6)alkyl$ or phenyl;
25 R^7 is H, $(C_1-C_6)alkyl$, $-C(O)-R^{16}$, $-C(O)OR^{17}$ or $-S(O)_2R^{17}$;
 R^8 , R^{10} and R^{11} are independently selected from the group consisting of R^1
 and $-OR^1$, provided that when the optional double bond shown in Formula II is
 present, R^{10} is absent;
 R^9 is H, OH or $(C_1-C_6)alkoxy$;
30 B is $-(CH_2)_{n_3}$ -, cis or trans $-(CH_2)_{n_4}CR^{12}=CR^{12a}(CH_2)_{n_5}$ - or
 $-(CH_2)_{n_4}C\equiv C(CH_2)_{n_5}$ -, wherein n_3 is 0-5, n_4 and n_5 are independently 0-2, and R^{12}
 and R^{12a} are independently selected from the group consisting of H, $(C_1-C_6)alkyl$
 and halogen;
 X is $-O-$ or $-NR^6-$ when the dotted line shown adjacent to X in Formula II
35 represents a single bond, or X is -OH or $-NHR^{20}$ when the bond is absent;

- 5 Y is =O, =S, (H, H), (H, OH) or (H, (C₁-C₆)alkoxy) when the dotted line shown adjacent to X in Formula II represents a single bond, or when the bond is absent, Y is =O, (H, H), (H, OH), (H, SH) or (H, (C₁-C₆)alkoxy);
each R¹³ is independently selected from H, (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, -(CH₂)_{n6}NHC(O)OR^{16b}, -(CH₂)_{n6}NHC(O)R^{16b}, -(CH₂)_{n6}NHC(O)NR⁴R⁵,
-(CH₂)_{n6}NHSO₂R¹⁶, -(CH₂)_{n6}NHSO₂NR⁴R⁵, and -(CH₂)_{n6}C(O)NR²⁸R²⁹ where
n₆ is 0-4, haloalkyl, and halogen;
- 10 each R¹⁴ is independently selected from H, (C₁-C₆)alkyl, -OH, (C₁-C₆)alkoxy, R²⁷-aryl(C₁-C₆)alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -(CH₂)_{n6}NHC(O)OR^{16b}, -(CH₂)_{n6}NHC(O)R^{16b},
-(CH₂)_{n6}NHC(O)NR⁴R⁵, -(CH₂)_{n6}NHSO₂R¹⁶, -(CH₂)_{n6}NHSO₂NR⁴R⁵, and
15 -(CH₂)_{n6}C(O)NR²⁸R²⁹ where n₆ is 0-4, halogen and haloalkyl; or
R¹³ and R¹⁴ taken together form a spirocyclic or a heterospirocyclic ring of 3-6 atoms;
wherein at least one of R¹³ or R¹⁴ is selected from the group consisting of
20 -(CH₂)_{n6}NHC(O)OR^{16b}, -(CH₂)_{n6}NHC(O)R^{16b}, -(CH₂)_{n6}NHC(O)NR⁴R⁵,
-(CH₂)_{n6}NHSO₂R¹⁶, -(CH₂)_{n6}NHSO₂NR⁴R⁵, and -(CH₂)_{n6}C(O)NR²⁸R²⁹ where
n₆ is 0-4;
- 25 R¹⁵ is H when the double dotted line shown adjacent to X in Formula II represents a single bond and is H, (C₁-C₆)alkyl, -NR¹⁸R¹⁹, or -OR¹⁷ when said bond is absent;
- R¹⁶ is independently selected from the group consisting of (C₁-C₆)alkyl, phenyl and benzyl;
- 30 R^{16b} is H, alkoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl-, R²²-O-C(O)-(C₁-C₆)alkyl-, (C₃-C₆)cycloalkyl, R²¹-aryl, R²¹-aryl(C₁-C₆)alkyl, haloalkyl, alkenyl, halosubstituted alkenyl, alkynyl, halosubstituted alkynyl, R²¹-heteroaryl, R²¹-(C₁-C₆)alkyl heteroaryl, R²¹-(C₁-C₆)alkyl heterocycloalkyl, R²⁸R²⁹N-(C₁-C₆)alkyl, R²⁸R²⁹N-(CO)-(C₁-C₆)alkyl, R²⁸R²⁹N-(CO)O-(C₁-C₆)alkyl, R²⁸O(CO)N(R²⁹)-(C₁-C₆)alkyl, R²⁸S(O)₂N(R²⁹)-(C₁-C₆)alkyl, R²⁸R²⁹N-(CO)-N(R²⁹)-(C₁-C₆)alkyl, R²⁸R²⁹N-S(O)2N(R²⁹)-(C₁-C₆)alkyl,

- 5 $R^{28}-(CO)N(R^{29})-(C_1-C_6)\text{alkyl}$, $R^{28}R^{29}N-S(O)_2-(C_1-C_6)\text{alkyl}$, $HOS(O)_2-(C_1-C_6)\text{alkyl}$,
 $(OH)_2P(O)_2-(C_1-C_6)\text{alkyl}$, $R^{28}-S-(C_1-C_6)\text{alkyl}$,
 $R^{28}-S(O)_2-(C_1-C_6)\text{alkyl}$ or hydroxy(C_1-C_6)alkyl);
 R^{17} , R^{18} and R^{19} are independently selected from the group consisting of
H, (C_1-C_6)alkyl, phenyl, and benzyl;
- 10 R^{20} is H, (C_1-C_6)alkyl, phenyl, benzyl, $-C(O)R^6$ or $-S(O)_2R^6$;
 R^{21} is 1 to 3 moieties independently selected from the group consisting of
H, -CN, -CF₃, -OCF₃, halogen, -NO₂, (C_1-C_6)alkyl, -OH, (C_1-C_6)alkoxy,
(C_1-C_6)-alkylamino-, di-((C_1-C_6)alkyl)amino-, $NR^{25}R^{26}(C_1-C_6)\text{alkyl-}$,
hydroxy- $(C_1-C_6)\text{alkyl-}$, -C(O)OR¹⁷, -C(O)R¹⁷, -NHC(O)R¹⁶, -NHS(O)₂R¹⁶,
15 -NHS(O)₂CH₂CF₃, -C(O)NR²⁵R²⁶, -NR²⁵-C(O)-NR²⁵R²⁶, -S(O)R¹³, -S(O)₂R¹³ and
-SR¹³;
 R^{22} is H or (C_1-C_6)alkyl;
 R^{23} is H, (C_1-C_6)alkyl, -C(O)R²⁴, -S(O)₂R²⁴, -C(O)NHR²⁴ or -S(O)₂NHR²⁴;
 R^{24} is (C_1-C_6)alkyl, hydroxy (C_1-C_6)alkyl or NR²⁵R²⁶-((C_1-C_6)alkyl)-;
- 20 R^{25} and R^{26} are independently selected from the group consisting of H and
(C_1-C_6)alkyl;
 R^{27} is 1, 2 or 3 moieties selected from the group consisting of H,
(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, halogen and -OH; and
 R^{28} and R^{29} are independently selected from the group consisting of H,
25 (C_1-C_6)alkyl, (C_1-C_6)alkoxy, R^{27} -aryl(C_1-C_6)alkyl, heteroaryl, heteroarylalkyl,
hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, heterocyclyl, heterocyclylalkyl, and
haloalkyl; or
 R^{28} and R^{29} taken together form a spirocyclic or a heterospirocyclic ring of 3-
6 atoms,
- 30 wherein said therapeutic condition is a cardiovascular or circulatory disease
or condition, an inflammatory disease or condition, a respiratory tract disease or
condition, cancer, acute renal failure, glomerulonephritis, astrogliosis, a fibrotic
disorder of the liver, kidney, lung or intestinal tract, Alzheimer's disease, diabetes,
diabetic neuropathy, rheumatoid arthritis, neurodegenerative disease, neurotoxic
35 disease, systemic lupus erythematosus, multiple sclerosis, osteoporosis,

- 5 glaucoma, macular degeneration, psoriasis, radiation fibrosis, endothelial dysfunction, a wound or a spinal cord injury, or a symptom or result thereof.
- 10 10. The method of claim 9 wherein the cardiovascular or circulatory disease or condition is atherosclerosis, restenosis, hypertension, acute coronary syndrome, angina pectoris, arrhythmia, heart disease, heart failure, myocardial infarction, thrombotic or thromboembolic stroke, a peripheral vascular disease, deep vein thrombosis, venous thromboembolism, a cardiovascular disease associated with hormone replacement therapy, disseminated intravascular coagulation syndrome, renal ischemia, cerebral 15 stroke, cerebral ischemia, cerebral infarction, migraine, renal vascular homeostasis or erectile dysfunction.
- 20 11. The method of claim 9 wherein the inflammatory disease or condition is irritable bowel syndrome, Crohn's disease, nephritis or a radiation- or chemotherapy- induced proliferative or inflammatory disorder of the gastrointestinal tract, lung, urinary bladder, gastrointestinal tract or other organ.
- 25 12. The method of claim 9 wherein the respiratory tract disease or condition is reversible airway obstruction, asthma, chronic asthma, bronchitis or chronic airways disease.
- 30 13. The method of claim 9 wherein the cancer is renal cell carcinoma or an angiogenesis related disorder.
- 35 14. The method of claim 9 wherein the neurodegenerative disease is Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease or Wilson's disease.
15. The method of claim 9 further comprising administering at least one therapeutically effective agent useful in the treatment of inflammation,

- 5 rheumatism, asthma, glomerulonephritis, osteoporosis, neuropathy and/or malignant tumors, angiogenesis related disorders, cancer, disorders of the liver, kidney or lung, melanoma, renal cell carcinoma, renal disease, acute renal failure, chronic renal failure, renal vascular homeostasis, glomerulonephritis, chronic airways disease, bladder inflammation,
- 10 neurodegenerative and/or neurotoxic diseases, conditions, or injuries, radiation fibrosis, endothelial dysfunction, periodontal diseases or wounds.
16. The method of claim 15 further comprising administering at least two therapeutically effective agents.

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